

# **Compressed Gas Drug Products - Electronic Drug Establishment Registration and Drug Listing in SPL Format**

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Lonnie Smith  
Project Manager  
FDA Data Standards Council



# SPL Standard

- The Structured Product Labeling (SPL) is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product information.
- American National Standards Institute (ANSI) accredited (SPL Release 4) – March 2009
- SPL is created using **EX**tensible **M**arkup **L**anguage

# XML & XSL Stylesheet

- XML – **EX**tensible **M**arkup **L**anguage
  - Relatively human-legible
  - Machine readable
  - Tags (elements) permit search of key information
- XML Documents – created via Notepad, Word Pad, XML validation tools, Xforms, etc...
- XSL Stylesheet – transforms the XML data to be viewed via web browser or printed documents

# SPL Stylesheet View/Source Code

## CONTRAINDICATIONS

Miracle Drug Injection is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

```
<component>
<section ID="_7CF4D228-65A6-6223-5A96-ECB4DBD620FC">
<id root="3A7D815A-A2B9-0389-5D92-4836E709B0FE" />
<code code="34070-3" codeSystem="2.16.840.1.113883.6.1" displayName="CONTRAINDICATIONS SECTION" />
<title mediaType="text/x-hl7-title+xml">CONTRAINDICATIONS</title>
<text><paragraph>Miracle Drug Injection is contraindicated in severe toxic central nervous system depression or comatose states from
any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.</paragraph></text>
<effectiveTime value="20070813" />
</section>
```

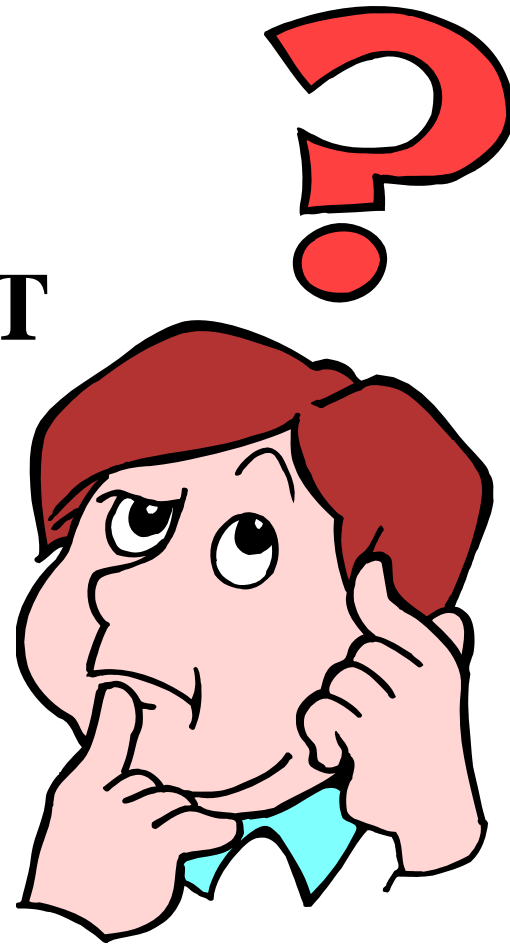
# ...three e-Files for Registration & Listing – SPL Format

- NDC Labeler Code Request
- Establishment Registration
- Content of labeling (CoL)/Listing

# Order of Submissions

1. NDC Labeler Request (LCR) and Establishment Registration (ER) SPL
  2. CoL/Listing SPL
- CoL/Listing validates against data submitted in NDC LCR and ER SPL

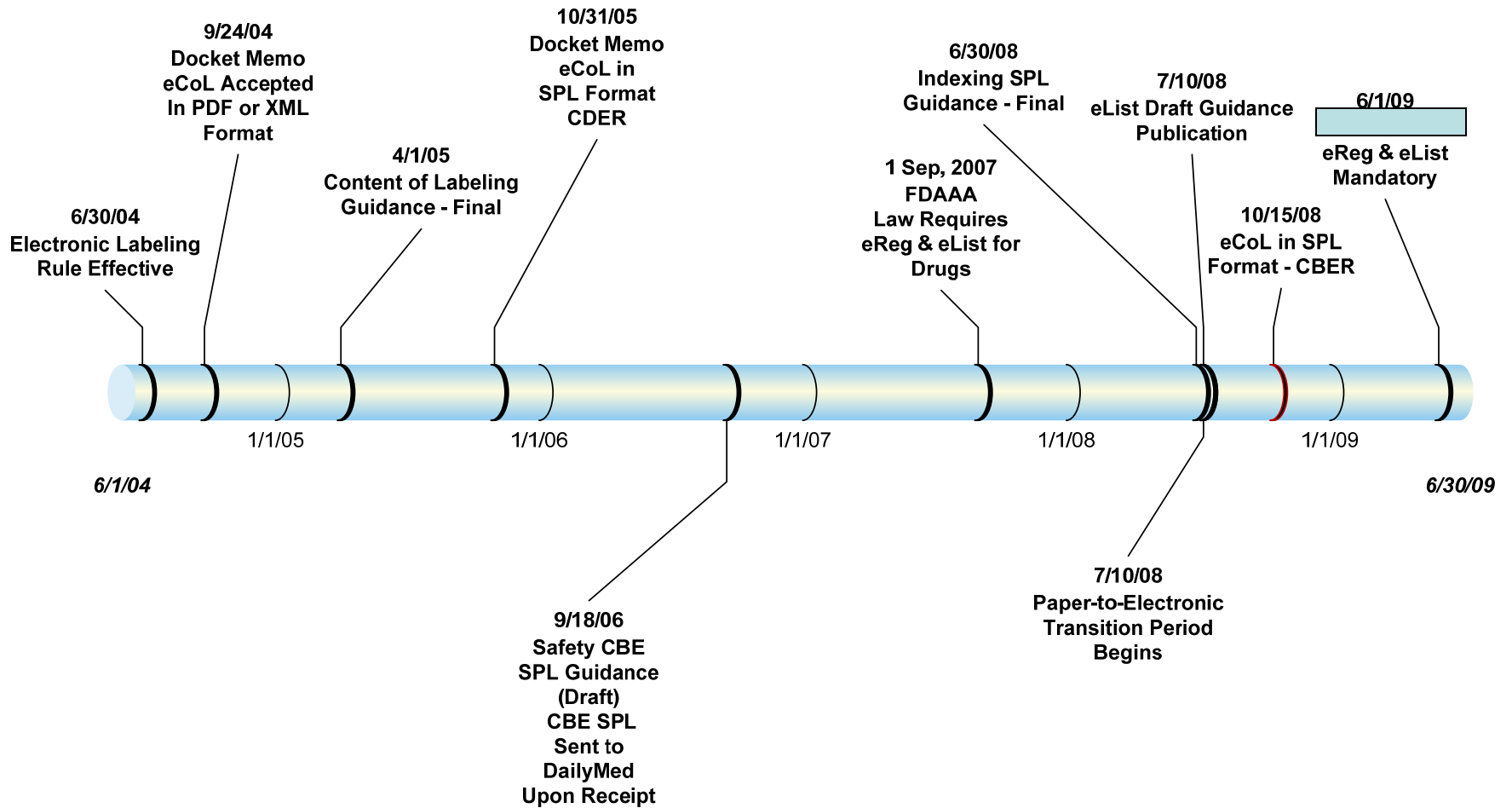
**WHY CHANGE  
THE DRUG LISTING  
AND ESTABLISHMENT  
REGISTRATION  
PROCESS THAT HAS  
WORKED FOR  
DECADES ????**



- Eliminate duplicative and redundant data entry
- Eliminate paper submissions
- Automate processing of data in a submission type in electronic format in a manner that FDA can adequately process, review, and archive.



## IMPLEMENTATION OF STRUCTURED PRODUCT LABELING AT FDA



# Transition from Paper to Electronic Drug Establishment Registration & Drug Listing

- Changes in FD&C Act require electronic registration of drug establishments and listing of human prescription drugs, OTC, animal drug, biologic products – September 2007
- Final guidance document for electronic drug establishment registration and listing – May 2009
- FDA has **adopted the use** of extensible markup language (XML) files in **SPL format** as the standard format for the **exchange of drug establishment registration & drug listing information**.

# Transitioning from Paper to Electronic: Drug Registration and Listing

- No more **PAPER** drug registration and drug listing as of June 1, 2009.
- Form 2656 – NDC Labeler Code & Establishment Registration – replaced with
  - NDC Labeler Code SPL
  - Establishment Registration
- Form 2657 – Drug Product Listing & Form 2658 – Private Labeler Distributor – replaced with
  - Content of Labeling/Listing SPL

# Benefits of Using SPL for Electronic Registration and Listing & Provision of Content of Labeling

- Electronic registration and listing process is more **efficient and effective** for industry and the Agency
- Accurate, up-to-date inventory of marketed drugs
- Eliminates data entry errors
- Eliminates the use of paper forms for listing and registration
- **24-hour submission window** – FDA Gateway
- Reduces the amount of time for FDA to receive and process your information.

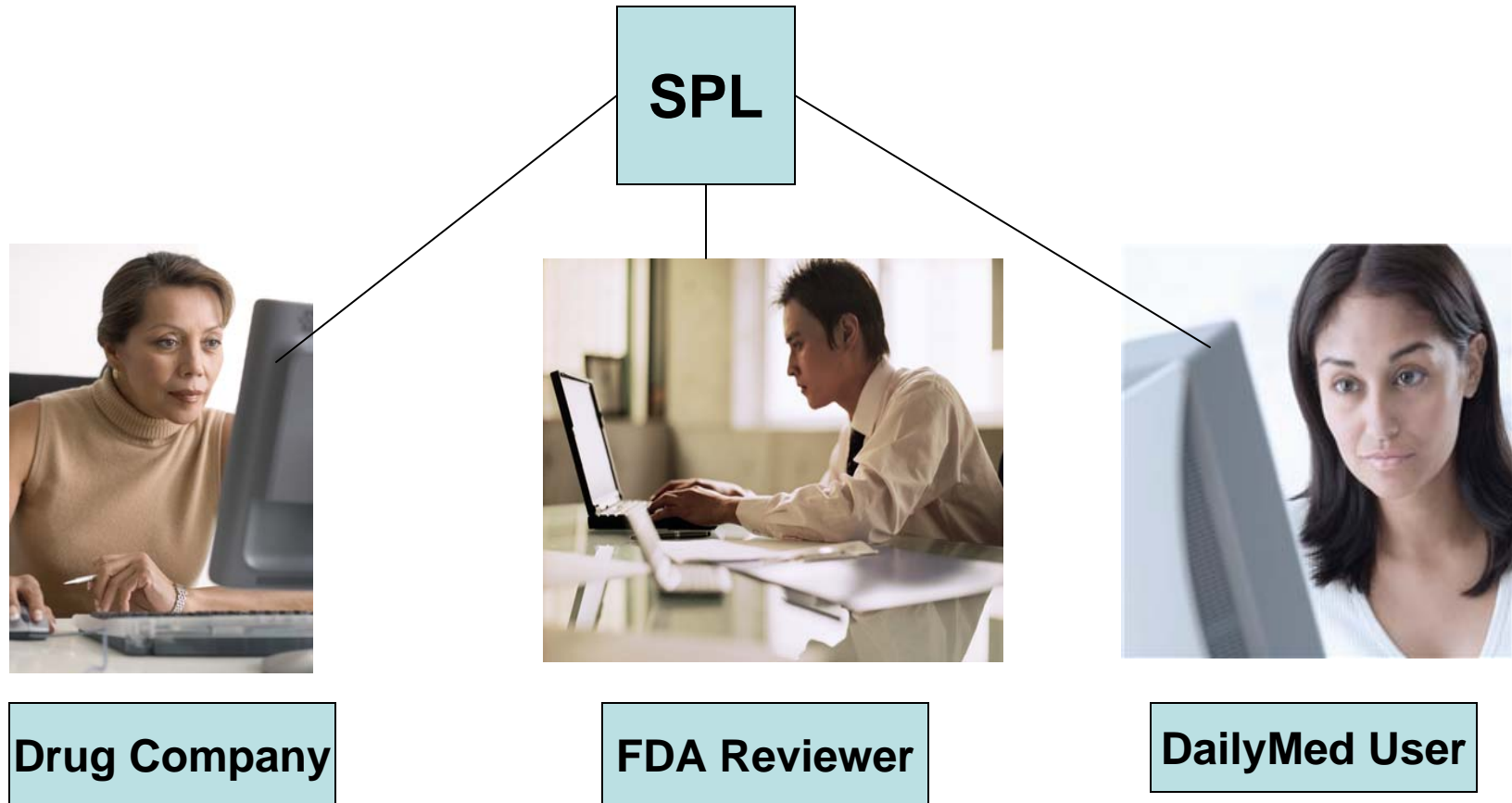
# More Benefits

- Well formed and properly created SPL files can be processed in minutes
- **Receive submission feedback in timely manner**
- Permits the relationship of data to eliminate need for manufacturer and distributor to list the identical drug products.
- Significant reduction in time for posting SPL on DailyMed

# Even More Benefits

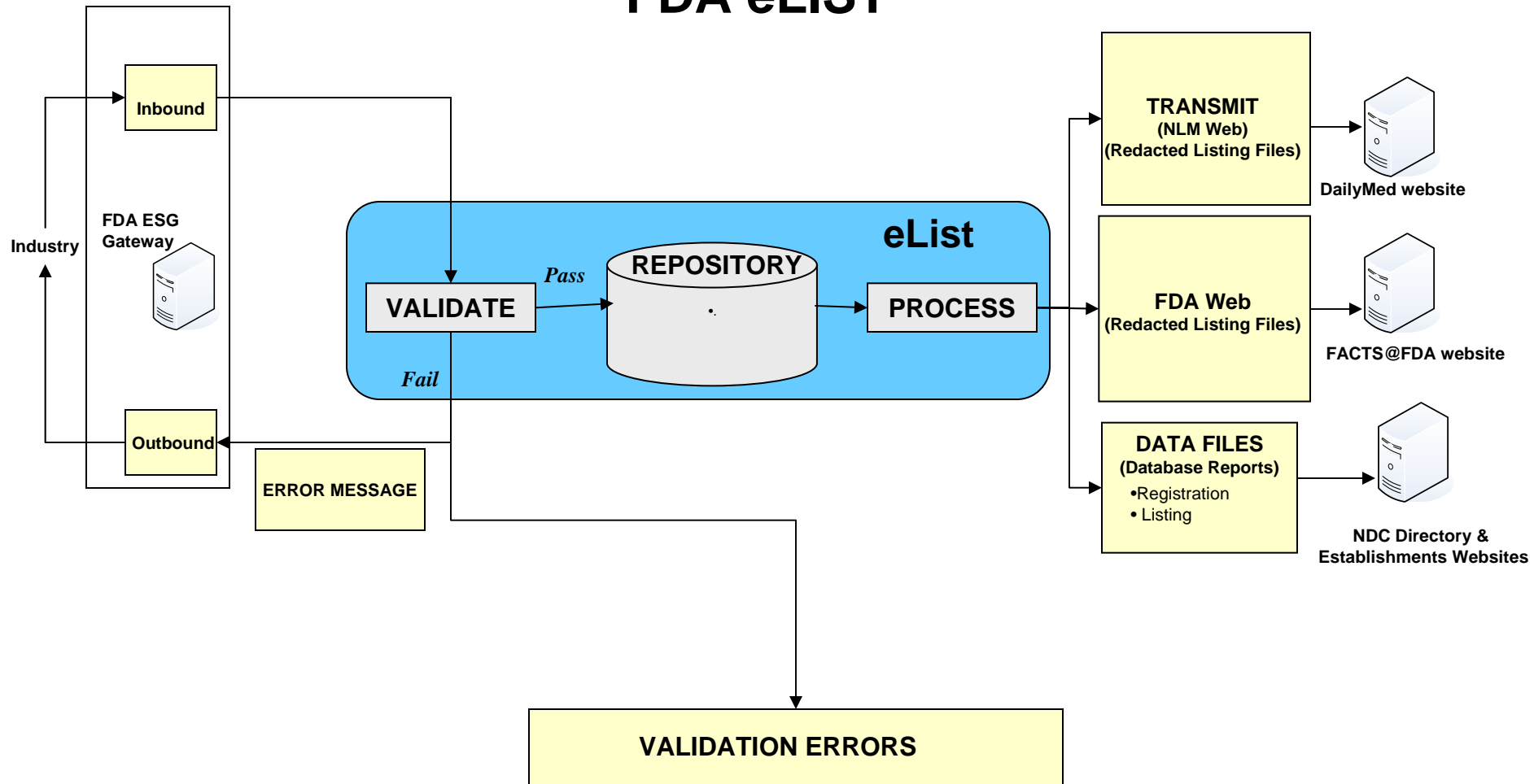
- Rapid parsing of data into FDA database
  - within seconds after validation
  - Minutes after receipt
- Significant reduction in time to post content of labeling & listing files on DailyMed
- Content of labeling and carton and container labeling rendered in one document

# Information Exchange SPL



**SPL is a standard that is used by drug companies, FDA and public to exchange or review or view product information. All three entities use computer or systems that “understand” SPL**

# FDA eLIST





# Administrative (Document Tracking Information)

## Basic information to identify the SPL document:

- **Document ID:** is a Globally Unique Identifier (GUID) and is unique for each version of the document. Letters used in a GUID are lower case.
- **Document Type:** The `<code>` is the LOINC code which provides information on the document type.
- **Effective Time:** provides a date reference to the SPL version including the year, month and day as `yyyymmdd`.
- **SetID:** is a GUID and is a unique identifier for the document that remains constant through all versions/revisions of the document.
- **Version number:** is an integer greater than zero that provides a sequence to the versions of the document.

# NDC Labeler Code Request Xforms View

HL7 SPL - NDC Labeler Code Request v 0.71	
<div>Open Save As Save</div>	
<div>NDC Labeler Code Request Preview</div>	
<b>Document Information</b>	
Type of document	NDC LABELER CODE REQUEST
ID	3267a844-378f-4020-912b-43babb77001d
Set ID	8d24aab5-8f91-42ca-9637-997a3d223e5c
Version Number	1
Effective Time	20080909
	example(YYYYMMDD)
<b>Labeler</b>	
Name	Acme Pharmaceuticals, Inc
DUNS Number	111119999
NDC Labeler Code	44444
<div>Add NDC Labeler Code Delete NDC Labeler Code</div>	
<b>Contact</b>	
Name	Charles Daniels
Mailing Address	44 Pembroke Drive
City	Rockville
State	MD
Country	USA
Postal Code	20888
Telephone Number	tel:+1-888-888-4757
Email Address	mailto:charles.daniels@acme-pharmaceuticals
	example(mailto:xportal@globalsubmit.com)

# NDC Labeler Code Request SPL Document

Acme Pharmaceuticals, Inc

<b>Product Information</b>	
<b>Product Type</b>	NDC LABELER CODE REQUEST

<b>Labeler -</b> Acme Pharmaceuticals, Inc (111119999) <b>NDC Labeler Code:</b> 44444			
<b>Contact</b>	<b>Address</b>	<b>Telephone Number</b>	<b>Email Address</b>
Charles Daniels	Address: 44 Pembroke Drive City, State, Zip: Rockville , MD, 20888 Country: USA	+1-888-888-4757	charles.daniels@acme-pharmaceuticals.com

Revised: 09/2008

Acme Pharmaceuticals, Inc

# NDC LCR SPL Scenarios

- **Requesting a new NDC Labeler Code**
  - Fill out the *NDC Labeler Code request* as described in sections 2.1 through 2.4 leaving the NDC Labeler Code field empty.
  - Requests for NDC Labeler Codes are individually evaluated prior to entry into the NDC System. The initial request will be automatically stopped because there is no NDC Labeler Code provided and is diverted to a FDA reviewer. Once the evaluation is completed, the response to the request is directed to the designated contact person.
  - Once the NDC Labeler Code is assigned, open the original SPL file and add the newly assigned NDC Labeler Code and resubmit the corrected file.
- **Initial electronic submission when NDC Labeler Code already assigned**
  - Fill out the *NDC Labeler Code request*. Only one NDC Labeler Code is included in an SPL file. In other words, use a different setId root for each NDC Labeler Code request.

# NDC LCR SPL

## Scenarios cont...

- **Correct SPL file validation error**
  - If an SPL file cannot be processed because of a validation error, a report on the validation error is sent from FDA to the contact person. Open the SPL file and correct the errors.
- **Correct a mistake in an SPL file just submitted**
  - Open the SPL file, correct the mistake, and fill in a **new id root** and **new version number** with the **original setId root** and the appropriate effective time.

# NDC LCR SPL

## Scenarios cont...

- **Update the NDC Labeler Code information**
  - Open the previous SPL file and fill in the new information without changing the other existing information. Fill in a **new id root** and **new version number** with the **original setld root** and the appropriate effective time.
- **Requesting a second NDC Labeler Code**
  - Only one NDC Labeler Code is associated with each *NDC Labeler Code request*. If a second NDC Labeler Code is requested, fill out a separate SPL file with a **different setld root**. The labeler information and contact information is the same as the SPL file for the first NDC Labeler Code request

# Notes

- Use NDC Labeler Code used in NDC Package Code (3-segment NDC)
- Submit NDC labeler codes that are used in NDCs associated with distributed products. (NDC on packaging)
- Only one NDC labeler code per NDC Labeler Code Request.
- NDC Labeler Code – Code should be identical to first segment of NDC (no leading zeros)

# Establishment Registration Data

- **Document Information**

- Type of Document
- ID
- Set ID
- Version Number
- Effective Time

- **Registrant**

- Name
- DUNS Number

- **Registrant Contact**

- Name
- Mailing Address
- City
- State
- Country
- Postal Code
- Telephone Number
- Email Address



# Establishment Registration Data (cont...)

- **Establishment**
  - Name
  - DUNS Number
  - FEI
  - Street Address
  - City
  - State
  - Country
  - Postal Code
  - Type of Operation(s)
- **Establishment Contact**
  - Name
  - Mailing Address
  - City
  - State
  - Country
  - Postal Code
  - Telephone Number
  - Email Address

# Establishment Registration Data (cont...)

- **US Agent**
  - Name
  - DUNS number
  - Telephone Number
  - Email Address
- **Importer (if applicable)**
  - Name
  - DUNS number
  - Telephone Number
  - Email Address

# Types of Operations

- Acceptable types of operations for establishments:
  - ANALYSIS
  - MANUFACTURE
  - RECOVERY
  - RELABEL
  - REPACK
- Unacceptable types of operations for establishments:
  - IMPORT
  - UNITED STATES AGENT

(as of February 2009)

# Importer

- *...under section 510(i)(1)(A) of the Act, the name of each importer that is known to the establishment (this means each U.S. company or individual in the United States that is an owner, consignee, or recipient, of the foreign establishment's drug, that is imported into the United States. An importer does not include the consumer or patient who ultimately purchases, receives, or is administered the drug, unless the foreign establishment ships the drug directly to the consumer or patient.); and the name of each person who imports or offers for import (this means the name of each agent, broker, or other entity, other than a carrier, that the foreign drug establishment uses to facilitate the import of their drug into the United States).*

*(from "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing")*

# Importer cont...

- May or may not be an importer for each foreign establishment

# US Agent

- Submission of information about US Agent replaces the paper letter
- Each foreign establishment in an ER SPL should have a US agent

# Establishment Registration

## SPL Xforms

### HL7 SPL - Establishment Registration v 0.71

Open Save As Save

Establishment Registration Preview

#### Document Information

Type of Document	ESTABLISHMENT REGISTRATION
ID	4ff69f20-6dc3-49ca-bb3c-0d589ff4c0b1
Set ID	118ec196-50d7-49b2-946a-831d29702818
Version Number	1
Effective Time	20080909

example(YYYYMMDD)

#### Registrant

Name	Acme, Inc.
DUNS Number	2223334441

#### Registrant Contact

Name	Deborah Tyler
Mailing Address	222 Bonifant Avenue
City	Fort Washington
State	PA
Country	USA
Postal Code	35295
Telephone Number	tel:+1-800-435-4585
Email Address	mailto:deborah.tyler@acme.com

example(tel:+1-201-555-1212)  
example(mailto:xportal@globalsubmit.com)

# Establishment Registration

## SPL Xforms cont...

<b>Establishment</b>		
Name	Acme Manufacturing, Inc.	
DUNS Number	475859252	
FEI	35295835928	
<input type="button" value="Add FEI"/> <input type="button" value="Delete FEI"/>		
Street Address	777 Sampson Street	
City	Mason	
State	PA	
Country	USA	
Postal Code	35859	
Type of Operation	manufacture ▼	
<input type="button" value="Add Type of Operation"/> <input type="button" value="Delete Type of Operation"/>		
<b>Establishment Contact</b>		
Name	Pam Jamison	
Mailing Address	777 Sampson Street	
City	Mason	
State	PA	
Country	USA	
Postal Code	35859	
Telephone Number	tel:+1-800-778-8359	example(tel:+1-201-555-1212)
Email Address	mailto:pam.jamison@acme.com	example(mailto:xportal@globalsubmit.com)
<input type="button" value="Add US Agent"/> <input type="button" value="Delete US Agent"/>		
<input type="button" value="Add Importer"/> <input type="button" value="Delete Importer"/>		



# Establishment Registration

## SPL Xforms cont...

<b>Establishment</b>		
Name	Acme International	
DUNS Number	98583572	
FEI	25835925829	
<input type="button" value="Add FEI"/> <input type="button" value="Delete FEI"/>		
Street Address	33 Bleu Rue	
City	Paris	
State		
Country	FRA	
Postal Code	20583	
Type of Operation	manufacture ▼	
Type of Operation	analysis ▼	
<input type="button" value="Add Type of Operation"/> <input type="button" value="Delete Type of Operation"/>		
<b>Establishment Contact</b>		
Name	Etienne St. Champs	
Mailing Address	33 Bleu Rue	
City	Paris	
State		
Country	FRA	
Postal Code	20583	
Telephone Number	tel:+33-538-5859	example(tel:+1-201-555-1212)
Email Address	mailto:etienne.st-champs@acme.com	example(mailto:xportal@globalsubmit.com)

# Establishment Registration SPL Document

Product Information	
Product Type	ESTABLISHMENT REGISTRATION

Registrant - Acme, Inc. (2223334441)			
Contact	Address	Telephone Number	Email Address
Deborah Tyler	Address: 222 Bonifant Avenue City, State, Zip: Fort Washington, PA, 35295 Country: USA	+1-800-435-4585	deborah.tyler@acme.com

Establishment			
Name	Address	ID/FEI	Operations
Acme Manufacturing, Inc.	Address: 777 Sampson Street City, State, Zip: Mason, PA, 35859 Country: USA	475859252	manufacture
Contact	Address	Telephone Number	Email Address
Pam Jamison	Address: 777 Sampson Street City, State, Zip: Mason, PA, 35859 Country: USA	+1-800-778-8359	pam.jamison@acme.com

# Establishment Registration

## SPL Document cont...

--	--	--	--

Establishment			
Name	Address	ID/FEI	Operations
Acme International	Address: 33 Bleu Rue City, State, Zip: Paris, 20583 Country: FRA	98583572	manufacture, analysis
Contact	Address	Telephone Number	Email Address
Etienne St. Champs	Address: 33 Bleu Rue City, State, Zip: Paris, 20583 Country: FRA	+33-538-5859	etienne.st-champs@acme.com
US Agent (ID)	Address	Telephone Number	Email Address
Acme USA (359582424)		+1-800-999-5542	jacob.goodman@acme.com
Importer (ID)	Address	Telephone Number	Email Address
Franklin Imports (252597793)		+1-888-444-5835	paula.johansen@franklin.com

Revised: 09/2008

# Electronically Registered Drug Establishments

- Example of actual Drug Firms Annual Registration Status Website Display

**Pfizer approved use of their name in presentation**

**Website address:** <http://www.accessdata.fda.gov/scripts/cder/drls/default.cfm>

Pfizer Ireland Pharmaceuticals	3003047405	300348730	Loughbeg Ringaskiddy, County Cork IRL	2008
Pfizer Ireland Pharmaceuticals	3003348730	986948909	Pottery Road, Dun Laoghaire Dublin IRL	2008
Pfizer Ireland Pharmaceuticals	3003382089	989811526	Little Island Cork IRL	2008
Pfizer Ireland Pharmaceuticals	3003882524	896090987	Ringaskiddy API Plant Cork IRL	2008
Pfizer Italia S.r.l.	3003637173	431227388	63046 Marino Del Tronto Ascoli Piceno (AP) ITA	2008
Pfizer Japan Inc	1000172081	705466860	Aza 5-Gochi, 2-banchi, Taketoyo-cho Chita-gun, Aichi-Ken Nagoya 470-2393 JPN	2008
Pfizer Laboratories Div Pfizer	1810508	006050075	100 Pfizer Drive, Kenilworth, NJ 07033 USA	2008

# Content of Labeling

- Compressed medical gas
  - Principal display panel section heading:
    - PACKAGE LABEL.PRINCIPAL DISPLAY PANEL
  - Image of the container label – (jpeg file)
  - Text from principal display panel

# Document Type

- HUMAN PRESCRIPTION DRUG LABEL

# Labeler & Establishment Data in Listing File

- **Labeler**
  - Name
  - DUNS Number
- **Establishment**
  - Name
  - DUNS number
  - Mark as Confidential
  - Type of operation
  - Product

# Listing Data cont...

- **Product Information**
  - Proprietary Name
  - Proprietary Name Suffix
  - Non-Proprietary Name
  - NDC Product Code
  - Dosage Form
  - DEA Schedule (if applicable)
  - Route(s) of Administration
- **Active Ingredient**
  - Name(s)
  - Unique Ingredient Identifier(s) (UNII)
  - Strength



# Listing Data cont...

- **Active Moiety**
  - Name(s)
  - Unique Ingredient Identifier(s) (UNII)
  - Basis of Strength

# Listing Data cont...

- **Packaging**
- **As ordered**
- **No asterisks permitted**
  - **Immediate packaging**
    - NDC Package Code (10 digit)
    - Quantity
    - Package Type
  - **Outer package**
    - NDC Package Code (10 digit)
    - Quantity
    - Package Type

# Listing Data cont...

- **Marketing Date**
  - Product Status
  - Start Marketing Date
  - End Marketing Date (if applicable)
- **Marketing Category**
  - Marketing Category
  - Application or citation number
  - Application or citation number code system

# **Product Data Elements**

# Product Data Elements

- Product
  - Product names
- Description
  - Ingredients
  - Strength
  - Dosage form
  - Route of administration
  - Controlled substance code
- How supplied
  - Packaged product

**Only terms in the controlled terminology are allowed.**

# Product Name and NDC Product Code

- The proprietary/trade and ingredient name data elements only include the name and do not include any additional qualifiers such as trademark symbols, route of administration, or dosage forms. (SPL R4 only: Suffix element may contain “XL” “ER”)
- The NDC product code in SPL documents is comprised of the first two segments of the NDC

**Proprietary name: “PROPRIETARY NAME”**

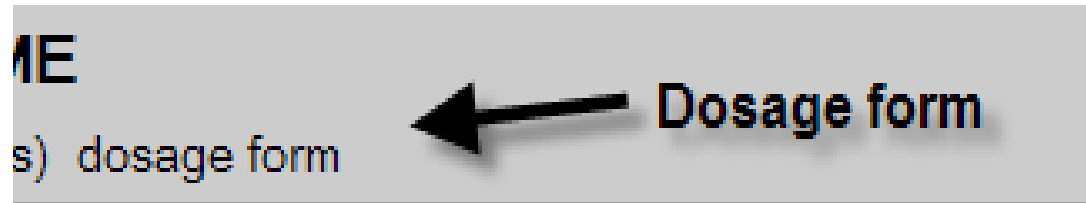
**Name of active ingredient: “name(s) of active ingredient(s)”**

**PROPRIETARY NAME**

name(s) of active ingredient(s) dosage form

# Dosage Form

- The dosage form is the name for the drug dosage form taken from the controlled terminology. Only terms in the controlled terminology are allowed.



# Route of Administration

- Labeled route of administration is the name of the route of administration taken from the controlled terminology. Only terms in the controlled terminology are allowed. A product may have one or more route of administration.
- For Compressed Medical Gas – RESPIRATORY (INHALATION)



# Active Ingredient

- The active ingredient includes the active ingredient name and identifier (Unique Ingredient Identifier (UNII) , strength, and the active moiety names and identifier (UNII). All active ingredients have at least one active moiety (in some cases two active moieties). Names of active ingredient **should not include designations such as USP or NF**. The name is taken from controlled terminology. Only terms in the controlled terminology are allowed. For ingredients, the controlled terminology is found in the FDA Substance Registration System/Ingredient Dictionary (SRS/ID). The **UNII is linked to the name** of the ingredient.
- Active moieties - more than one active moiety can be included for each active ingredient.

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
name(s) of active ingredient(s) (name of active moiety number 1 and name of active moiety number 2)	name(s) of active ingredient(s)	50 mg

# Strength of Ingredient

- SPL R4 documents will allow companies to **designate strength based on the active ingredient, active moiety.**

## Example

Numerator: 0.4 **mL**

Denominator: 1 **L**

# Marketing Category

- Select the appropriate marketing category for the drug product.

Marketing Information	
Marketing Category	
unapproved medical gas	

# Application or Citation Number Field

- There is no application or citation number for compressed medical gas

# Marketing Status & Date

- The marketing status describes the activity of the product
- The expiration date of the last lot released to the marketplace.

# Marketing Status & Dates

- Status of product
  - **Active:** on the market
  - **Completed:** when marketing is done the drug is no longer going to be available on the market.
  - Active or completed timestamp: effectiveTime value.
- Low value
  - Time on the market
  - Determines release of CoL/Listing SPL to public
- High value
  - Time off the market (e.g. the expiration date of the last lot released to the market.)

Marketing Start Date	Marketing End Date
01/24/2005	

# Common Errors in eList Pilot Program Submissions

- XML file sent not enclosed within a folder
- XML file name is not the document ID root name
- Spaces before telephone number
- Hyphens in DUNS number
- SPL file created with outdated SPL xforms
- Two-character country code used in place of three-character country code (ISO-3166 - <ftp://ftp1.nci.nih.gov/pub/cacore/EVS/FDA/SPL/>)

**QUESTIONS?**